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Review

Non-variceal upper gastrointestinal bleeding

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INTRODUCTION

Non-variceal upper gastrointestinal bleeding (UGIB) remains a common and challenging emergency for gastroenterologists and general physicians. The annual incidence is 50 to 150 per 100,000 of the population, and, even though there have been significant improvements in endoscopic and supportive therapies, the overall mortality stubbornly remains around 10%, and may even reach 35% in hospitalised patients with serious co-morbidity. Patients aged over 80 years of age now account for around 25% of all UGIB and 33% of UGIB occurring in hospitalized patients and therefore tend to account for much of the poor outcome of this condition.[1]

The causes of non-variceal UGIB are shown in (*Table I*), although the commonly quoted figure of 50% for peptic ulcer bleeding may be overestimated. In a recent large CORI (Clinical Outcome Research Initiative) study of UGIB, peptic ulcer was the probable cause of UGIB in only 20% of cases.[2] The incidence of peptic ulcer disease is expected to continue to decline with more widespread helicobacter pylori eradication and proton pump inhibitor (PPI) usage.

RISK ASSESSMENT AND INITIAL MANAGEMENT

Several clinical scoring systems e.g. Rockall score, the Baylor bleeding score, the Cedars-Sinai Medical Centre Predictive Index and the Blatchford score, have been developed to direct appropriate patient management and enable cost effective use of resources. These systems weigh a combination of clinical, laboratory and endoscopic variables to produce a score that predicts the risk of mortality, recurrent haemorrhage, need for clinical intervention or suitability for early discharge. Factors commonly associated with poor outcome from UGIB may be related to the patient's presentation and co-morbidities, or to the behaviour of the ulcer (*Table II*). Risk stratification using non-endoscopic parameters has the advantage that it can be performed readily on initial presentation in the emergency department, and appropriate initial risk assessment is still possible, even if early endoscopy, which requires skilled staff and resources, is not always available.

Inclusion of endoscopic stigmata of recent haemorrhage (SRH) that relate to increased risk of re-bleeding and death into scoring systems increases the sensitivity for predicting patients at high or low risk compared to non-endoscopic assessments.[3-5] High risk lesions such as actively bleeding ulcers, non-bleeding visible vessels (NBVV) and adherent clots (*Table III*) require effective aggressive intervention to reduce re-bleeding which is associated with a 5-16 fold increase in mortality.[6,7] The re-bleeding rate of ulcers with a clean base or red or blue spots are low and endoscopic intervention is usually not recommended.[8-10] In fact, early endoscopy-based triage may permit safe and early discharge of "low risk" patients with no increased rate of re-bleeding or mortality.[11]

Endoscopic SRH, particularly NBVV and flat pigmented spots, can be difficult to differentiate.[12] Doppler assessment is unlikely to be widely available for some time because of technical and resource

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TABLE I

Causes of non-variceal UGIB

Diagnosis	*Incidence [%]*
Peptic ulcer	20 – 50
Mallory-Weiss tear	15 – 20
Erosive gastritis/ duodenitis	10 – 15
Oesophagitis/ oesophageal ulcer	5 – 10
Malignancy	1 – 2
Angiodysplasia/ vascular malformations	5
Other	5

TABLE II

Predictors of adverse outcome from UGIB

Patient:	Shock
	Melaena
	Significant fresh blood in vomit, gastric aspirate or rectum
	Sepsis
	Anaemia at presentation
	Cardiac/ liver/ renal disease
Ulcer:	Large ulcer size
	Persistent bleeding despite endoscopic therapy
	Recurrent bleeding

TABLE III

Forrest classification of peptic ulcers in UGIB

Forrest class	*Type of lesion*	*Risk of rebleed if untreated [%]*
Ia	Arterial spurting	100
Ib	Arterial oozing	17-100
IIa	Visible vessel	8-81
IIb	Sentinel clot	14-36
IIc	Haematin covered flat spot	0-13
III	No stigmata	0-10

limitations, but may be effective at differentiating between patent vasculature and pigmented spots.[13] In this study there was agreement between the endoscopic Forrest classification and Doppler assessment in only 58% of cases, suggesting that Doppler was more sensitive at detecting high-risk lesions. Re-bleeding, requirement for surgery and mortality rate were all significantly lower in the Doppler-assessed endoscopically treated group.

Resuscitation and management of medical co-morbidities, often in intensive care or high dependency, remains the mainstay of the initial management of patients prior to endoscopy. The presence of blood-stained nasogastric aspirate can be used to predict the presence of high risk lesions and nasogastric tube insertion should be considered for some patients.[14] The role of endotracheal intubation remains controversial; the benefits are easier endoscopy and reduced risk of massive aspiration in patient with a reduced level of consciousness, but evidence of a reduction in acquired pneumonia or cardiopulmonary events is lacking.[15,16]

ENDOSCOPIC MANAGEMENT

Endoscopic intervention reduces the rate of re-bleeding, need for surgical intervention and mortality in high risk patients with UGIB.[17] The optimum timing of endoscopy remains a balance between clinical need and resources, but endoscopy performed within 24 hours of hospital admission has been shown to reduce the length of hospital stay and may reduce the likelihood of re-bleeding or surgical intervention in the highest risk patients.[18] Not infrequently, excessive blood in the upper GI tract may preclude an accurate endoscopic diagnosis in a small number of patients. These patients have a significantly higher rate of complications, rebleeding, need for surgery and mortality.[19] Bolus administration of intravenous erythromycin prior to endoscopy has been shown to clear the stomach of blood, increase the likelihood of successful haemostasis and reduce the need for subsequent interventions.[20,21]

Most haemostatic techniques are equally effective when used alone, although doubt has been cast on the value of "stand alone" therapy with adrenaline injection. Recent focus has been directed towards combination therapies and mechanical means of homeostasis. Injection of dilute (1:10 000) adrenaline in 1ml aliquots around the bleeding points has traditionally been the main method of haemostasis in Europe, whereas application of heat is the preferred strategy in the United States. Adrenaline injection results in haemostasis in up to100% of patients with bleeding peptic ulcers, probably by a combination of vascular tamponade and vasoconstriction, with a concomitant reduction in re-bleeding rates from 40 to 15%.[22,23] The dose of adrenaline required to achieve haemostasis is variable but larger volumes (13-20ml vs. 5-10ml) in high risk patients (Forrest type I or IIa lesions) results in less re-bleeding (15.4% vs. 30.8%).[24] Although injection with adrenaline is successful in achieving initial haemostasis, 15-36% of patients rebleed, a figure that is unacceptably high.[25,26]

Sclerosants such as ethanol, polidocanol and ethanolamine are equally effective as adrenaline but carry more risk.[25,27-29] In one study, ethanol injection alone was shown to have a re-bleeding rate as low as 4%;[30] however, most other published studies have achieved similar haemostasis to adrenaline alone. Combination therapy with adrenaline and ethanol may improve haemostasis and shorten hospital stay for patients with spurting haemorrhage.[28]

The evidence for thrombin injection is mixed with differing reports of effect on clinical outcomes.[31-33] Repeated daily injection of fibrin glue following treatment with dilute adrenaline in patients with active bleeding or NBVV until the ulcer base is clean or covered is expensive but reduces re-bleeding although not mortality rates.[34]

N-butyl-2-cyanoacrylate (Histoacryl) injection has been shown to be effective for control of variceal bleeding,[35] but its role in non-variceal UGIB remains uncertain. In a small study of 32 patients with bleeding ulcers, Histoacryl injection was no more effective than injection with dilute adrenaline.[25] More recently, Lee *et al* demonstrated significantly lower re-bleeding rate for patients with Forrest type Ia lesions treated with Histoacryl compared to injection with hypertonic saline-adrenaline injection.[36] However, there was no overall benefit in the use of Histoacryl with regards to haemostasis rates, emergency surgery or mortality. Arterial embolisation is a recognized complication of this treatment and means that this therapy is recommended as a measure of last resort because of potentially fatal adverse effects.

In contrast to injection techniques, thermal haemostasis is achieved by compression of the artery during heating (coaption) and/or the

effect of heat on tissue. The only non-contact thermal techniques currently available are Argon Plasma Coagulation (APC) and laser (Nd:YAG). APC involves conduction of a high frequency electrical current through a beam of ionized argon gas, resulting in superficial tissue damage and coagulation. A prospective observational study of APC in 254 patients with non-variceal UGIB revealed initial haemostasis rates of 75.9% and re-bleeding rates of 5.7%.[37] The addition of a second haemostasis technique increased successful haemostasis to 99.6%. The only comparative randomised trial involving APC alone with heater probe was underpowered, although rates of haemostasis, rebleeding, emergency surgery and 30 day mortality were similar for the two techniques.[38] A larger prospective randomised study of dual therapies for bleeding peptic ulcers showed no significant difference in primary haemostasis, procedure duration, re-bleeding, requirement for surgery, 30-day mortality or ulcer healing at 8 weeks between treatment with adrenaline and heater probe versus adrenaline and APC.[39] ND:YAG laser therapy has been shown to be as effective than injection with adrenaline-polidocanol,[40] but, due to technical constraints of the technique, laser therapy is not routinely used in the management of non-variceal UGIB.

In contrast to APC and laser, Bipolar Electrocoagulation (BPE) and Heater Probe Thermocoagulation (HPT) use thermal contact to achieve haemostasis by compression of the vessel and coaption. BPE devices sometimes include an injector/irrigator component (e.g. Gold probe, Boston Scientific, MA), which allows injection of adrenaline or irrigation of the lesion. BPE reduces the re-bleeding rate when compared with normal saline injection in high risk bleeding ulcers,[41] and compared to medical therapy when used in combination with adrenaline in Forrest IIb ulcers.[42] Combination therapy with HPT and adrenaline in the treatment of actively bleeding peptic ulcers resulted in haemostasis in up to 98.6%, with re-bleeding in 8.2%,[43] although added benefit is confined to high risk lesions.[26] When used alone, HPT was not superior to combination treatment with adrenaline and polidocanol in patients with Forrest type I, IIa and IIb ulcers.[44] There is no incremental benefit of adding thrombin to HPT in patients with bleeding peptic ulcers with regards to haemostasis, re-bleeding rates, requirement for surgery, adverse events or mortality.[45]

Mechanical haemostasis with endoloops or clips, e.g. the Hemoclip (Teleflex Medical, PA), has an increasing role in the control of non-variceal UGIB. Endoclips are deployed on a visible vessel to achieve vascular compression and can achieve homeostasis in up to 100% of cases.[46] Comparative studies suggest lower re-bleeding rates than adrenaline injection,[47] ethanol[48] or saline/adrenaline injection.[49] The additional benefit of adrenaline with a mechanical method is unclear,[50] although one randomised comparative study of combination epinephrine-polidocanol injection and Hemoclip versus Hemoclip alone for bleeding peptic ulcers showed clipping to be inferior to combination therapy.[51] Two small studies have evaluated Hemoclips for control of bleeding due to Dieulafoy's lesion, demonstrating a trend towards reduction in the need for repeat procedures.[52,53] Hemoclips can be technically difficult to apply if the ulcer is relatively inaccessible, for instance high on the gastric lesser curve or on the posterior duodenal wall. In fact, application of a clip with successful haemostasis in either of these locations has been as low as 30% in published series. Rotatable, versatile endoclips that can deploy multiple and/or stronger clips are needed.

Endoscopic band ligation (EBL) is currently technically easier to use than endoclips and has been shown to be safe and effective for control of small lesions in a small series of acute peptic ulcer bleeding[54] and with bleeding due to Dieulafoy's lesions.[55]

ADHERENT CLOTS

Subgroup analysis of patients with adherent clots in early endoscopic studies demonstrated little or no benefit of endoscopic therapy for ulcers with adherent clots.[56-59] However, a subsequent meta-analysis showed significant benefit in the group of patients with active bleeding or NBVV.[17] To further address this issue, a recent controlled trial in patients with severe UGIB and adherent clot randomised 32 patients to "medical" or combination endoscopic therapy following clot removal.[42] Endoscopic therapy consisted of adrenaline injection, shaving of the clot with cold guillotine and BPE of the underlying ulcer SRH. Combination endoscopic therapy was safe and associated with less early re-bleeding compared to medical therapy, although the small sample size, unexpectedly low re-bleed rates in the combination therapy group [0%] and unequal distribution of confounding

factors in the two groups means that caution needs to be taken when extrapolating the results. Also, even in clinical trials there tends to be significant intra-observer variation in the labelling of SRH and the degree clot "adherence" depending on the method of removal employed.[60,61] For instance, in one study five minutes of irrigation via a bipolar probe was found to remove clot in 43% of patients, whereas irrigation with a syringe via the endoscope channel only removed 9% of clots.[62] Placement of a transparent irrigating hood over the endoscope tip that allows forceful irrigation yet maintains a reasonable endoscopic view may prove useful for clot removal and may reduce total procedure time.[63,64] Although the optimum technique for clot removal is unclear, clot removal should be attempted as high risk SRH may be exposed in the underlying ulcer in around a further 30% of patients. Current practice among experienced endoscopists involves targeted irrigation and possibly snare guillotine of an adherent clot followed by treatment of the underlying lesion.[42]

Finally, a variety of endoscopic suturing devices have been developed primarily for gastroplication in patients with gastro-oesophageal reflux. Endoscopic suturing for UGIB management is an attractive prospect, but further development of new devices is required before endoscopic suturing for UGIB can be widely adopted.

"SECOND-LOOK" ENDOSCOPY AND ENDOSCOPIC RE-TREATMENT

Routine "second look" endoscopy, in the absence of established rebleeding or patient instability, has gone out of vogue after studies showed no benefit with regards to clinically significant outcomes for unselected patient populations,[65] although there may be a role in high risk patients.[66,67] Repeat therapeutic endoscopy may be indicated (depending on local endoscopic and surgical expertise) if there is clinical evidence of re-bleeding or if the initial therapeutic procedure was unsuccessful or partially successful.[10,68] In expert hands, endoscopic re-treatment is associated with fewer complications and no increased mortality risk compared to surgery.[69]

ACID SUPPRESSION

In vitro studies of the effect of gastric pH on platelet aggregation and coagulation provide the rationale for acid suppression in UGIB. If gastric pH is maintained above pH6 (by infusional PPI), platelet aggregation is optimized and fibrinolysis relatively inhibited, thereby potentially improving the likelihood of clot stability at an ulcer site. Individual trials of H2 receptor antagonists (H2RA) have generally failed to demonstrate a clinical benefit in UGIB,[70] although one meta-analysis has suggested a weak effect.[71] A recent consensus statement suggested that the available data on H2RAs does not support their use in ulcer bleeding.[10]

Several studies have evaluated intravenous proton pump inhibitors (PPI) for non-variceal UGIB; unfortunately, these trials are heterogeneous in terms of patient population, regimen of PPI and timing/type of endoscopic intervention, making comparisons difficult. However, meta-analyses of PPIs in non-variceal UGIB have now shown a benefit in terms of re-bleeding and need for surgery, but not for mortality.[2,72-75] The usual intravenous regime for omeprazole therapy in the more robust studies was an 80mg intravenous bolus of omeprazole followed by a continuous infusion of 8mg/hour for up to 72 hours. This regimen resulted in a reduction of rebleeding from 22.5% to 6.7%, representing a NNT of 6 to prevent one person bleeding within 30 days.[74] Subsequent studies using lower intravenous doses of omeprazole[76] or high dose oral omeprazole[77-79] also demonstrated a reduction in rebleeding rate. Further study is required to determine the optimum dose, route of administration and dosing schedule of PPI in UGIB. In the meantime, and with the evidence currently available, it seems appropriate to treat patients with high risk peptic ulcers with intravenous or high dose oral PPI after endoscopic therapy has been administered.

FUTURE DIRECTIONS IN ENDOSCOPY

Endoscopic suturing has already been mentioned earlier in this article. Currently available suturing devices are somewhat awkward to use and are not suitable for management of bleeding, although the principle of suturing peptic ulcers to control bleeding is well established in surgery. Further development is required before suturing becomes possible in the endoscopic sphere.

The risks associated with application of heat to bleeding lesions are due to the requirement for tissue contact, lack of control of depth of injury and difficulty in treating multiple or diffuse lesions. Gastric freezing to achieve haemostasis during variceal and non-variceal bleeding has been possible for several decades although evidence of therapeutic

benefit from the original techniques was lacking and delivery systems were clumsy.[80] However, recent delivery of new liquid nitrogen or nitrous oxide delivery systems has made endoscopic cryotherapy feasible although still experimental.[81-83] Cryotherapy using nitrous oxide relies on the Joule-Thompson effect: rapid expansion of compressed gas results in a drop in temperature of the gas. The resultant "no contact" therapy has been tested in proctitis and may also be possible in upper gastrointestinal lesions.

CONCLUSIONS

Non-variceal UGIB remains a significant cause of morbidity and mortality. Patients at high risk can be identified by risk assessment scoring systems that include clinical and endoscopic variables. Adequate resuscitation, aggressive endoscopic therapy and PPI therapy are effective for achieving haemostasis and preventing adverse clinical outcomes, although the effect on mortality is low. Multidisciplinary care, including endoscopists, surgeons, intensivists and radiologists early in the assessment and decision stages, is vital to optimise care.

CONFLICT OF INTEREST

The authors have no declared conflict of interest.

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